IUD with levonorgestrel and galactorrhoea

Introduction

The intra-uterine device (IUD) with levonorgestrel is used as *contraception*, *for the treatment of strengthened menstrual bleeding or menorrhagia* and *as adjuvant progestogen to prevent endometrial hyperplasia during estrogen therapy in the peri- and post menopause*. The levonorgestrel-releasing IUD (Mirena®) consists of a polyethylene T-shaped reservoir containing levonorgestrel. The in vivo release rate of levonorgestrel is initially approximately 20 µg/24 hours and declines to 10 µg/24 hours after 5 years. Levonorgestrel levels are detectable in serum with a maximum concentration 2 weeks after insertion. The median serum concentration decreases from 206 pg/ml to 194 pg/ml after 6 months and 131 pg/ml after 12 months [1]. In comparison, administration of intramuscular depot medroxyprogesterone 150 mg gives a plasma concentration of approximately 1 ng/ml [2]. For oral levonorgestrel/ethinylestradiol 0.15/0.03 mg maximum plasma levels of 3 ng/ml levonorgestrel are reached approximately 1 hour after intake. Total plasma levels are highly dependent of sex hormone binding globulin concentrations [3].

Galactorrhoea has been defined as “milk secretion by the mammary gland which is not the result of pregnancy, as well as a more than six month post-partum milk secretion in a woman who is not breastfeeding”. As well as in physiological lactation, estrogens and prolactin are involved in galactorrhoea. Prolactin is a polypeptide hormone that is synthesized in, and secreted from, specialized cells of the anterior pituitary gland. Thyrotropin-releasing hormone and estrogens are important prolactin releasing factors (PRF), dopamine is an inhibitor of PRF. The secretion of prolactin is mainly regulated by ongoing induction by dopamine. Important stimulating factors of the milk discharge belong to the estrogens. They influence the function of dopamine and also have a direct stimulating effect on the anterior pituitary gland [4,5].

The current observation describes the possible association between IUD with levonorgestrel and galactorrhoea.

Reports

On July 3rd 2013, the Netherlands Pharmacovigilance Centre Lareb had received 11 reports concerning galactorrhoea associated with the use of IUD with levonorgestrel. No information was reported on prolactin levels or whether the insertion of the IUD was post-partum. Seven reports were made by healthcare professionals and four by patients. The mean age of the patients is 38 years. A positive dechallenge was reported in one patient (E). Three patients recovered without dosage changes (B, G, H). Time to onset varied from 2 days till 10 years after start.

Table 1. Reports of galactorrhoea associated with the IUD with progestogens

Patient, Number, Sex, Age, Source	Drug, daily dose Indication for use	Concomitant Medication	Suspected adverse drug reaction	Time to onset, Action with drug outcome

Patient, Number, Sex, Age, Source	Drug, daily dose Indication for use	Concomitant Medication	Suspected adverse drug reaction	Time to onset, Action with drug outcome
A 43188 F, 44 General Practitioner	levonorgestrel IUD		galactorrhoea	not reported dose not changed unknown
B 46360 F, 41 – 50 years Specialist doctor	levonorgestrel IUD contraception	liothyronine, levothyroxine	breast tenderness, galactorrhoea	9 months dose not changed recovered
C 66529 F, 21 – 30 years General Practitioner	levonorgestrel IUD contraception		galactorrhoea	4 months unknown unknown
D 71828 F, 11-20 years Pharmacist	levonorgestrel IUD		galactorrhoea	2 years unknown unknown
E 77856 F, 21-30 years Consumer	levonorgestrel IUD		headache, ovarian cyst, memory impaired, paraesthesia hand, galactorrhoea, depressed mood	6 weeks withdrawn recovering
F 79870 F, 21-30 years Consumer	levonorgestrel IUD contraception		abdominal pain, breast hyperplasia, breast pain female, galactorrhoea	4 years unknown unknown
G 84269 F, 21-30 years General Practitioner	levonorgestrel IUD contraception		galactorrhoea, breast disorder nos, nausea	weeks dose not changed recovered
H 86262 F, 31-40 years General Practitioner	levonorgestrel IUD contraception	citalopram	galactorrhoea	1 month dose not changed recovered
I 117727 F, 31-40 years Consumer	levonorgestrel IUD contraception		weight loss, sleep disorder, alopecia, oedema, loss of libido ageusia, feeling cold, constipation, palpitations, acne, psychiatric disorder nos, memory impairment, arthralgia, dizziness, hepatic function disorder, paresthesia hand, galactorrhoea, dyspnea, hyperhidrosis, headache	2 days drug withdrawn not recovered at time of reporting

Patient, Number, Sex, Age, Source	Drug, daily dose Indication for use	Concomitant Medication	Suspected adverse drug reaction	Time to onset, Action with drug outcome
J 139477 F, 31-40 years Consumer	levonorgestrel IUD contraception escitalopram 10 mg anxiety		galactorrhoea	1 month not reported not recovered at time of reporting
K 149577 F, 31-40 years General Practitioner	levonorgestrel IUD contraception	salmeterol/ fluticasone	galactorrhoea	10 years dose not changed not recovered at time of reporting

For patient B it was reported that prolactin levels were normal. A CT-scan showed no microprolactinoma. After treatment with bromocriptine the patient recovered. Patient F described that she has the feeling that the symptoms 'followed the pattern of her ovulation'; breast hyperplasia and galactorrhoea appear every month.
Patient H has a medical history of gastric bypass because of overweight, gestational hypertension, arthropathy, depression and migraine.

Other sources of information

SmPC

Galactorrhoea is not described in the SmPC of IUD with levonorgestrel [1]. For other contraceptives that only contain a progestogen, galactorrhoea is described in the SmPC of oral and intramuscular medroxyprogesterone [2,6]. It is not described in the SmPC of the desogestrel containing 'mini pill' [7].
For second generation contraceptives, containing a progestogen and estrogen, galactorrhoea is described [3]. In this case the galactorrhoea is said to be most probably caused by the estrogen component.

Literature

A Medline search revealed no information on galactorrhoea in association with the use of IUD with levonorgestrel. One study was found describing galactorrhoea in association with the use of depot progesterone 150 mg. Omar et al. have noticed that over the last few years an increased number of patients using medroxyprogesterone mentioned complaints of galactorrhoea. A review of the clinical data showed that between 1999 and 2005, 360 adolescents used medroxyprogesterone for at least 6 months. After medical follow-up, 13 adolescents developed galactorrhoea. With exception of one patient, prolactin levels were normal. It is therefore thought the galactorrhoea is a progesterone related effect [8].

Databases

On July 3rd 2013, the database of Netherlands Pharmacovigilance Centre Lareb contained 11 reports of galactorrhoea associated with the use of IUD with levonorgestrel. The reporting odd ratio (ROR) for these 11 reports is disproportional, ROR = 6.8 (95% confidence interval (CI) 3.7 – 12.4). The WHO database of the Uppsala Monitoring Centre contained 220 reports on

'galactorrhoea' associated with the use of IUD with levonorgestrel. The ROR for this database is disproportional, ROR = 2.9 (95% CI 2.5 – 3.3). The Eudravigilance database of the EMA contained 37 reports of galactorrhoea associated with IUD with levonorgestrel. The ROR for this database is disproportional, ROR = 2.4 (95% CI 1.8 – 3.4). Table 2 shows the number of reported cases of galactorrhoea association with the use of IUD with levonorgestrel with the corresponding ROR in the database of Lareb, the WHO and Eudravigilance.

Table 2. Reports of galactorrhoea associated with IUD with levonorgestrel in the database of the Netherlands Pharmacovigilance Centre Lareb, WHO and Eudravigilance

Drug	Number of reports	ROR (95% CI)
IUD with levonorgestrel and galactorrhoea	Lareb: 11	6.8 (3.7 – 12.4)
	WHO: 220	2.9 (2.5 – 3.3)
	Eudravigilance: 37	2.4 (1.8 – 3.4)

Prescription data

The number of IUD with levonorgestrel users in the Netherlands is shown in table 3 [9].

Table 3. Number of women using IUD with levonorgestrel (Mirena®) in the Netherlands between 2008 and 2012*

	2008	2009	2010	2011	2012
IUD with levonorgestrel	83,809	87,713	96,478	20,708	19,843

* The table is based on GIP data which show the number of users of an IUD that have the product reimbursed under the Health Insurance Act. In 2011, reimbursement was restricted to) women under 21 y, or 2) treatment of endometriosis according to Dutch treatment guidelines, or 3) treatment of menorrhagia with reference values according to guidelines. Therefore, the table does not show the total number of users.

Mechanism

Galactorrhoea is caused by an increase of prolactin levels. As dopamine is an inhibitor of PRF, decrease of dopamine levels can result in galactorrhoea. Galactorrhoea may also be the result of disorder such as hypothyroidism or malignancies [4,5].

Gupta et al. studied the role of catecholamines in the mechanism of antiovulatory and other central effect of medroxyprogesterone in adult rats. A single dose of medroxyprogesterone (100mg/kg) given intramuscularly did not cause any significant change in brain catecholamine levels after 7 days of treatment. However, there was a significant reduction in brain dopamine levels after 15 days of medroxyprogesterone administration [10].
In literature conflicting results about the effect of progestogens on prolactin secretion were found. Mijiddorj et al. [11] studies the effect of sex steroid hormones on basal prolactin promoter activity in GH3 cells (clonal strain of rat pituitary tumor cells which can synthesize and secrete prolactin). Their study showed that the basal prolactin promoter activity was significantly decreased by both estrogen and progesterone. However, in a study of ovariectomized rats, DeMaria et al. [12] found that both estrogen and progesterone negatively influenced the activity of neuroendocrine dopaminergic neurons and increased prolactin secretion. Further, Haug et al. [13] demonstrated that estrogen stimulated prolactin release, whereas

progesterone decreases prolactin production as well as inhibiting the stimulatory effect of estrogen on the GH3 cells.

Discussion and conclusion

Lareb received 11 reports concerning galactorrhoea associated with the use of IUD with levonorgestrel. Latencies were not very consistent and varied between days and years after insertion of the IUD with levonorgestrel, with a median of 4 months. Of the cases reported to Lareb outcome was reported seven times. A positive dechallenge was reported for one patient. Further, three had recovered without dosage changes. In the cases reported to Lareb no information was given about prolactin levels or whether the insertion of the IUD was post-partum.
This association is statistically supported by the database of Lareb and the WHO. A mechanism by which levonorgestrel causes galactorrhoea is not elucidated. In literature conflicting results about the effect of progestogens on the prolactin secretion were found. Galactorrhoea is described in the SmPC of second generation contraception pills. Here, the galactorrhoea is said to be most probably caused by the estrogen component. It is remarkable that the reports we described here are of galactorrhoea in association with only a progestogen. However, for some progestogen containing drugs galactorrhoea is described in the SmPC.

- Galactorrhoea should be mentioned in the SmPC of IUD with levonorgestrel.

References

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After evaluation of this signal, the Marketing Authorisation Holder of Mirena® informed Lareb on January 21 2014 of the following: *It is the company's view that the information presented by Lareb provides no sufficient evidence to include galactorrhoea in the Core Safety Information for Mirena. In Mirena users with non-puerperal galactorrhea, other causes should be investigated.*

This signal has been raised on 31 October 2013. It is possible that in the meantime other information became available. For the latest information please refer to the website of the MEB www.cbgmeb.nl/cbg/en/default.htm or the responsible marketing authorization holder(s).